REMARKS/ARGUMENTS

Claims 38, 40-41, 46, and 48 are under examination. Claims 1-37, 39, 42-45, and 47 have been canceled without prejudice. Claim 38 has been amended to better define the subject matter which Applicants regard as the invention. Support is found throughout the specification, particularly, on page 17, lines 23-24. No new matter has been introduced with this Amendment.

Claim Rejections under 35 USC 112:

Enablement:

Claims 38, 40-41, 46 and 48 are rejected under 35 USC 112, first paragraph, because the specification, while being enabling for *in vitro*, does not reasonably provide enablement for *in vivo*. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's allegation. As pointed out in the responses to the previous office actions, Applicants maintain that the present case represents an example where the claimed invention is based on the data obtained in an *in vitro* assay (cytoadherence assay) which has been well accepted as a standard assay in the art for studying *Plasmodium* life cycle. The cytoadherence assay is based on the fact that the phenomenon of cytoadherence is essential for parasite survival and virulence. In treating subjects with severe malaria, it is important to rapidly reduce the pathology associated with cytoadherence as well as kill parasites *per se*. Since it is not possible to measure cytoadherence directly *in vivo*, in a subject parasitized by *Plasmodium*, the data obtained from the cytoadherence assay *in vitro* have been considered by those skilled in the art as predictive of the *in vivo* activity.

The cytoadherence assay is discussed in detail on pages 1-3, item 3, in the enclosed Declaration by Dr. Nicolas Anstey. It has been known that in patients with moderately severe or severe malaria, parasitized red blood cells adhere via endothelial cell receptors to the lining of microvascular blood cells and obstruct blood flow. Ho *et al.* (*Infection and Immunity* 1991, 59:873-878), enclosed herewith as Exhibit D, clearly

show that the *in vitro* cytoadherence assay using C32 human melanoma cells was useful in predicting *in vivo* disease severity (see page 876, right column, first full paragraph). Also enclosed is another article by Udomsangpetch *et al.* (*J. Infectious Disease* 1996, 173:691-198, Exhibit E) in which the authors used in vitro cytoadherence assays to evaluate the ability of anti-malarial drugs to alleviate or prevent pathologic adherence processes in malaria. Therefore, Applicants submit that the as-filed specification does enable those skilled in the art to make and use the claimed invention, i.e., a method of inhibiting cytoadherence of parasitized cells in a subject parasitized by a Plasmodium species by administering an agent such as L-arginine. This is consistent with the provision in MPEP 2164.02 regarding the issue of correlation between *in vitro* or *in vivo* model assays and a claimed method of use where it is specifically stated that "...if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate...".

In order to further demonstrate that the claimed invention is indeed enabled, i.e., the inventive method works *in vivo* in malarial patients, not merely an *in vitro* method to treat parasitized red blood cells, as alleged by the Examiner, Applicants submit a Declaration by Dr. Nicholas M. Anstey which describes the results of a clinical trial recently carried out in Indonesia.

The clinical trial described in the Declaration was conducted to test, *inter alia*, the safety and efficacy of L-arginine in the treatment of moderately severe *falciparum* malaria in hospitalised patients. Because direct *in vivo* measurement of a reduction in cytoadherence is not possible in human subjects with moderately severe malaria, efficacy of L-arginine was evaluated using peripheral arterial tonometry (PAT) which is a non-invasive tool to assess endothelial function. The PAT measures the capacity of blood vessels to dilate in response to obstructed blood flow, which is caused by cytoadherence of parasitized cells in malarial patients. In an earlier study at the same hospital (also described in the Declaration) the PAT analysis was shown to provide an accurate measure of malarial severity useful for evaluating the effects of anti-malarial

treatments. As stated in more detail in the Declaration, a portion of subjects hospitalised with moderately severe malaria exhibited impaired endothelial function which is a useful measure for evaluating changes in cytoadherence-induced patholy, as determined by PAT. After L-arginine administration, there was a dose related improvement of 35% in endothelial function. Nitric oxide production was also measured as exhaled nitric oxide (NO) after L-arginine administration and the results showed a 55% increase in exhaled NO.

The results of the clinical trial demonstrate that L-arginine infusion up to 12g is safe and can improve NO production and endothelial function in adult patients with moderately severe malaria. Accordingly, L-arginine or NO gas can be used for treatment of severe malaria in which NO production and endothelial functional are even more impaired than in subjects with moderately severe malaria.

In view of the new data presented in the Declaration, the Examiner's allegation that the specification does not teach how to extrapolate data obtained from the *in vitro* assay to the development of effective *in vivo* human treatment, commensurate in scope with the claimed invention, is no longer applicable.

In summary, Applicants submit that the as-filed specification provides sufficient description to enable those skilled in the art to make and use the claimed invention. Withdrawal of the rejection under 35 USC 112, first paragraph is respectfully requested.

Written Description:

Claims 38, 40-41, 46 and 48 are further rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Office Action states that "...as discussed above, the skilled artisan cannot envision the instant invention, particularly the in vitro data of cytoadherence, is an adequate extrapolation of the in vivo situation. Adequate written description requires

more than a mere statement that is part of the invention and reference to a potential method of isolating it..."

Applicants respectfully submit that the rejection based on the alleged written description deficiency is not appropriate in the present case and that the as-filed specification does convey to those skilled in the art that the inventors had possession of the claimed invention at the time of filing of the priority application. It is noted that the issues raised in relation to the written description requirement are those raised in the enablement rejection and that In view of the above remarks and the new data presented in the Declaration, those issues are considered to be no longer relevant.

Withdrawal of the rejection under 35 USC 112, first paragraph, is respectfully requested.

Claim Rejections under 35 U.S.C. 102:

Claims 38, 40, 46 and 48 are further rejected under 35 USC 102(b) as allegedly anticipated by Rockett et al. Claims 38, 40, 46 and 48 are further rejected under 35 U.S.C. 102(e) as allegedly anticipated by Stamler et al. Applicants respectfully traverse this rejection.

Without acquiescing to this rejection, claim 38 has been amended such that the claimed method is for inhibiting cytoadherence of parasitized cells in a subject parasitized by a *Plasmodium* species by administering an agent such as L-arginine, NO gas and/or an S-nitrosothiol compound. Neither Rockett et al. nor Stamler et al. teach the invention.

The Examiner states that Rockett *et al.* teach using S-nitrosoglutathione or S-nitrocysteine for killing of *Plasmodium in vitro* which would inhibit or reduce cytoattachment on the target red blood cell, and thus diminish the pathological adherence of the parasitized red blood cell (the Examiner refers page 3281, right

column, third paragraph). The Examiner notes that inhibitory concentrations of these compound are provided. Our review of the cited passage indicates that the closest suggestion to the above alleged teaching is on page 3281, third paragraph which states that reactive nitrogen intermediates may lead to inactivation of enzymes or changes in protein function. Applicants submit that this is not a clear reference to the claim. The citation as a whole is clearly directed to reporting the killing of *Plasmodium falciparum in vitro* from an S-nitrosothiol compound. The reference fails to teach inhibiting cytoadherence or inhibiting or reducing pathological adherence properties of parasitized cells in malarial patients and accordingly fails to anticipate the claimed invention.

The Office Action points out that Stamler *et al* teach a method of treating the infected *Plasmodium* falciparum patient *ex vivo* by using a nitrosothiol compound such as S-nitrocysteine or S-nitroglutathione. In contrast, the instant invention is a method of inhibiting cytoadherence of parasitized cells in a subject, i.e., *in vivo*, using L-arginine, NO gas, and/or an S-nitrosothiol compound. In addition, as far as Stamler et al. refer to *in vivo* administration of nitrosothiol compounds, this was limited to the treatment of sickle cell anaemia. The method of the present invention is clearly distinct from the method taught by Stamler.

The Examiner has further alleged (see page 10 of the Office Action) that Stamler *et al.* also teach using S-nitrosothiol compounds to treat infectious disease (at column 2, lines 5 to 15) and therefore that the claims are anticipated. However, Applicants respectfully disagree and set forth the following comments.

Applicants submit that it is clear in amended claim 38 that the method is intended to be applicable *in vivo* and does not encompass *ex vivo* treatment. The claim is directed to "...inhibiting the cytoadherence of parasitized cells in a subject...comprising administering to said subject an agent...".

With regard to the Examiner's allegation that Stamler *et al.* at column 2, lines 5 to 15, anticipates claim 38, Applicants submit that this passage merely makes a statement

regarding the general knowledge about NO and does not provide any link to the claimed invention. This passage cannot be seen as a disclosure of killing *Plasmodium* species parasites either *in vitro* or *in vivo* nor can it fairly be read as a teaching that S-nitrosothiol compounds inhibit cytoadherence of *Plasmodium* parasitized cells sufficient to inhibit or reduce pathologic adherence properties of such cells. Therefore, the claimed invention is not anticipated by Stamler *et al.*

Based on the above, claims 38, 40, 46, and 48 are not anticipated by either Rockett et al. or Stamler et al. Withdrawal of the rejection under 35 USC 102 is respectfully requested.

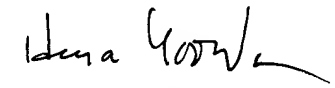
Conclusion:

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are further issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by a Petition for Extension of Time (3 months), a Request for Continued Examination, a Declaration under 37 CFR 1.132 and the requisite fees ($395.00 for RCE and $510.00 for three months extension as required under 37. C.F.R. 1.17). It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount enclosed is incorrect, however, please deduct from Deposit Account 07-1969 the appropriate fee for this submission and any extension of time required.

Respectfully submitted,



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